CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215206Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
ARIA Sufficiency Memo

Date:	September 27, 2021
Reviewer:	Dinci Pennap, PhD, MPH, MS Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Deputy Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concern
Drug Name:	Qulipta™ (atogepant)
Application Type/Number:	NDA 215206
Applicant/sponsor:	AbbVie, Inc.
OSE RCM #:	2021-1431

A. Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Atogepant (Qulipta, AbbVie Inc.) is a selective, orally administered, calcitonin-gene related peptide (CGRP) receptor antagonist with the proposed indication (b) (4) CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology and evidence suggests that selective CGRP receptor antagonists may have clinical benefit during migraine attacks when CGRP levels are elevated. Several agents that act on the CGRP pathway have been approved by the FDA for the treatment of migraine. Monoclonal antibodies (erenumab, galcanezumab, fremanezumab, and eptinezumab) that target CGRP, or its receptor have been approved for the preventive treatment of migraine in the United States. These drugs are administered subcutaneously or intravenously. Two orally administered small molecules in the same drug class as atogepant have been approved for the acute treatment of migraine (ubrogepant and rimegepant) and most recently, rimegepant was also approved for the preventive treatment of episodic migraine.

The recommended dosage for atogepant is 10 mg, 30 mg, or 60 mg once daily. For patients with severe renal impairment or end-stage renal disease, the recommended dosage is 10 mg daily. Atogepant has an elimination half-life of approximately 11 hours and its mean apparent oral clearance is approximately 19L/hr. Following a single oral dose of 50 mg in healthy male subjects, 42% and 5% of the dose was recovered as unchanged atogepant in feces and urine, respectively.

The Sponsor conducted two long-term multicenter open-label safety studies in the United States (Studies 3101-302-002 and 3101-309-002), to evaluate the safety and tolerability of treatment with atogepant 60 mg once daily when administered over 52 weeks and 40 weeks, respectively, for the preventive treatment of migraine in participants with episodic migraine. As of the 25th of May 2020 (cut-off date), 655 participants were enrolled in study 3101-309-002 and have taken at least dose of atogepant.

Two deaths were recorded in these studies and assessed as unrelated to atogepant use. A 26-year-old woman taking atogepant 60 mg daily developed a viral infection, followed by myositis (muscle inflammation), and subsequent death due to overwhelming group A streptococcus infection. The second death was ruled a homicide and unrelated to atogepant. The most common treatment emergent adverse events in atogepant treated patients were constipation, nausea, decreased appetite, and fatigue/somnolence. While there were no cases of severe liver injury or jaundice, there were some cases of serum transaminase elevations that appeared to be causally associated with atogepant use. All cases were resolved after discontinuation of atogepant. Overall, the percentage of serum transaminase elevations over 3 times the upper limit of normal were similar between treatment arms and placebo (1% versus 1.8%). Atogepant-treated patients experienced weight loss at a greater frequency than patients treated with placebo. On average, patients on atogepant 60 mg daily, experienced 0.94 kg (2.1 pounds) weight loss at the end of blinded treatment, compared to a 0.44 kg (0.97 pound) weight gain in patients treated with placebo. These adverse reactions have been added to Section 6 of the label. No increased risk was noted in the

atogepant database for vascular ischemic events. The risk of adverse outcomes in pregnancy has not been characterized. Safety and efficacy in pediatric migraine patients has also not been established.

1.2. Describe the Safety Concern

As part of a New Drug Application, the Division of Neurology 2 requested that the Division of Epidemiology assess the sufficiency of the FDA's Active Risk Identification and Analysis (ARIA) for broad-based signal detection studies of atogepant use for migraine attacks during pregnancy.

The potential risk of inadvertent in-utero exposure to medications is well established and drug-related fetal safety concerns remain unabated among female patients of childbearing potential.[1] In the United States, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[2] Women, compared with men, have a 1-year migraine prevalence nearly threefold higher (17 vs. 6%) and lifetime incidence more than twofold higher (43 vs. 18%).[3,4] Further, menarche, menstruation, pregnancy, menopause and use of oral contraceptives and of hormone replacement treatment may influence migraine occurrence suggesting that the potential risk of fetal exposure is heightened among patients receiving treatments for migraine.

The Sponsor conducted two adequately and well controlled trials (*Study CGP-MD-01 and Study 3101-301-002*) that provide substantial evidence of efficacy for the preventive treatment of episodic migraine and two long-term safety studies (*Studies 3101-302-002 and 3101-309-002*). Data on pregnancy exposure during clinical trials are insufficient to inform the risk of maternal, fetal, and infant outcomes associated with the use of atogepant. Women who were pregnant or lactating were excluded from atogepant clinical studies. Fifteen pregnancies were reported among atogepant users across all four studies and details of gestational weeks of exposure were not provided. Among patients who received 30mg atogepant daily in the safety population in *Study CGP-MD-01*, one patient had a healthy infant at full term and another patient had a premature delivery at week 36. Details of the health status of the premature baby are not provided. In the same study, a third patient, a 19-year-old woman who received atogepant 60 mg daily for 82 days elected to terminate her pregnancy on day 96 (no reason was given).

Two patients randomized to receive 10mg atogepant daily in Study *3101-301-002* became pregnant during the study and were treated for 8 and 21 days, respectively. Both patients gave birth to full-term healthy infants. Eight pregnancies were recorded among patients who received 60 mg atogepant daily in the long-term safety study *3101-302-002*. No pregnancy outcome information was provided for four of these pregnancies. Two of the eight pregnancies have no recorded doses; one ended in a spontaneous abortion and the other pregnancy resulted in a full-term healthy infant. One patient who received atogepant 60mg and esomeprazole 40 mg had an elective termination (no reason was given) and another patient had an infant at full term who spent 6 days in the NICU for low blood sugar, low blood potassium, and jaundice. Details of gestational weeks of atogepant exposure were not provided.

In addition, two pregnancies were recorded in long-term safety study *3101-309-002*. One patient had a spontaneous abortion, and no pregnancy outcome information was provided for the other patient. Details of gestational weeks of atogepant exposure were not provided.

In non-clinical studies of male and female rats prior to and during mating and continuing in females to gestational day 7, oral administration of atogepant (0, 5, 20, or 125 mg/kg/day) resulted in no adverse effects on fertility or reproductive performance. Plasma exposures (AUC) at the highest

dose tested (125 mg/kg/day) were greater than 10 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal body weight and skeletal ossification at the two highest doses. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development in rats, plasma exposure (AUC) was approximately 4 times that in humans at the MRHD. Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose, which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, maternal plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

In pregnant rabbits, exposure to oral atogepant (0, 30, 90, or 130 mg/kg/day) during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested, which was not associated with notable maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development in rabbits, maternal plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Overall, there is limited information to assess risk to the mother or fetus with use of atogepant during pregnancy.[a]

In the proposed draft product labeling for atogepant as of September 22, 2021, the Risk Summary in Section 8 states:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of QULIPTA in pregnant women. In animal studies, oral administration of atogepant during the period of organogenesis (rats and rabbits) or throughout pregnancy and lactation (rats) resulted in adverse developmental effects (decreased fetal and offspring body weight in rats; increased incidence of fetal structural variations in rabbits) at exposures greater than those used clinically [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The estimated rate of major birth defects (2.2% -2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

[a] QULIPTA (atogepant). Draft clinical review dated August 25, 2021. Division of Neurology 2. U.S. Food and Drug Administration

Published data have suggested that women with migraine may be at increased risk of preeclampsia and gestational hypertension during pregnancy.

Data

Animal Data

Oral administration of atogepant (0, 5, 15, 125, or 750 mg/kg/day) to pregnant rats during the period of organogenesis resulted in decreases in fetal body weight and skeletal ossification at the two highest doses tested (125 and 750 mg/kg), which were not associated with maternal toxicity. At the no-effect dose (15 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 4 times that in humans at the maximum recommended human dose (MRHD) of 60 mg/day.

Oral administration of atogepant (0, 30, 90, or 130 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in an increase in fetal visceral and skeletal variations at the highest dose tested (130 mg/kg/day), which was associated with minimal maternal toxicity. At the no-effect dose (90 mg/kg/day) for adverse effects on embryofetal development, plasma exposure (AUC) was approximately 3 times that in humans at the MRHD.

Oral administration of atogepant (0, 15, 45, or 125 mg/kg/day) to rats throughout gestation and lactation resulted in decreased pup body weight at the highest dose tested (125 mg/kg/day), which persisted into adulthood. At the no-effect dose (45 mg/kg/day) for adverse effects on pre- and postnatal development, plasma exposure (AUC) was approximately 5 times that in humans at the MRHD.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child-bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †
☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group (i.e., registry study)
☒ Pregnancy registry with external comparison group (i.e., registry study)
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☒ Electronic database study with chart review (i.e., complementary study)
☐ Electronic database study without chart review
☒ Other, please specify: Alternative study designs would be considered: e.g., retrospective cohort study using claims or electronic medical record data with outcome validation or a case-control study. (i.e., complementary study)

2.4. Which are the major areas where ARIA is not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: ARIA lacks access to medical records. The pregnancy registry being considered requires that an expert clinical geneticist or dysmorphologist review and classify medical records of all major congenital malformations. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.
Analytical Tools: ARIA data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal and fetal outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The DN2 requests two PMR studies related to pregnancy outcomes; the proposed language, as of

September 14, 2021, is as follows:

> "Conduct a prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to atogepant during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to atogepant before or during pregnancy, and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life."
>
> "Conduct a pregnancy outcomes study using a different study design than provided for the pregnancy registry study above (for example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to atogepant during pregnancy compared to an unexposed control population."

References

1. Wyszynski DF, Shields KE. Frequency and type of medications and vaccines used during pregnancy. *Obstet Med.* 2016;9(1):21-27.
2. Dinatale M. The pregnancy and lactation labeling rule (PLLR). 2016; https://www.fda.gov/media/100406/download. Accessed September 9, 2021.
3. Stewart W, Wood C, Reed M, Roy J, Lipton R. Cumulative lifetime migraine incidence in women and men. *Cephalalgia.* 2008;28(11):1170-1178.
4. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68(5):343-349.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DINCI D PENNAP
09/27/2021 10:50:45 AM

KIRA N LEISHEAR
09/27/2021 10:59:20 AM

SUKHMINDER K SANDHU
09/27/2021 11:16:38 AM

JUDITH W ZANDER
09/27/2021 11:23:49 AM

PATRICIA L BRIGHT
09/27/2021 11:33:59 AM

ROBERT BALL
09/27/2021 01:26:35 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 20, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215206
Product Name and Strength:	Qulipta (atogepant) tablet, 10 mg, 30 mg, 60 mg
Applicant/Sponsor Name:	AbbVie Inc.
OSE RCM #:	2021-211-2
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Abbvie, Inc. submitted revised container labels and carton labeling received on September 16, 2021 for atogepant. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a], and an email request to submit revised labels and labeling to include the recently approve proprietary name, Qulipta.

2 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The readibility of the proprietary name can be improved. We provide recommendations for Abbvie, Inc. in Section 3, below.

3 RECOMMENDATIONS FOR ABBVIE INC.

We recommend the following be implemented prior to approval of this NDA:

a. The presentation of the letter "Q" in the proprietary name, Qulipta, can be improved for readability. The artistic presentation of the letter "Q" may detract from the readability

[a] Morris, C. Label and Labeling Review for Qulipta (NDA 215206). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUL 16. RCM No.: 2021-211-1.

and may distort the interpretation of the proprietary name. We recommend you reconsider the font or styling used in the presentation of the proprietary name.

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
09/20/2021 02:07:17 PM

STEPHANIE L DEGRAW
09/20/2021 02:19:43 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 14, 2021

To: Heather Fitter, M.D.
Division of Neurology II (DN II)

Daniel Ngembus, Regulatory Project Manager, (DN II)

Tracy Peters, Associate Director for Labeling, DNP

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for atogepant tablets, for oral use

NDA/BLA: 215206

In response to DN II consult request dated July 26, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA for atogepant tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DN II (Daniel Ngembus) on September 1, 2021, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on September 8, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 30, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

23 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAMUEL A FASANMI
09/14/2021 04:11:27 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 8, 2021
To:	Daniel Ngembus, PharmD Regulatory Project Manager **Division of Neurology II (DN2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Nyedra W. Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Samuel Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (atogepant)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215206
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On January 28, 2021, AbbVie, Inc. submitted for the Agency's review an original New Drug Application (NDA 215206) for TRADENAME (atogepant). The proposed indication is for the preventive treatment of migraine in adults with less than 15 migraine days per month.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN2) on August 11, 2021 and July 26, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (atogepant) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (atogepant) PPI received on January 28, 2021, and received by DMPP and OPDP on September 1, 2021.
- Draft TRADENAME (atogepant) Prescribing Information (PI) received on January 28, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 1, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E CARROLL
09/08/2021 01:07:04 PM

SAMUEL A FASANMI
09/08/2021 01:14:13 PM

NYEDRA W BOOKER
09/08/2021 01:42:28 PM

LASHAWN M GRIFFITHS
09/08/2021 01:47:47 PM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 17, 2021

To: Nicholas Kozauer, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Ph.D., Director
Controlled Substance Staff

From: Chad J Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

Subject: Atogepant (AGN-241689/MK-8031) NDA 215206
Qulipta 10, 30, and 60 mg oral tablets
IND Number: 114780
Indication(s): (b) (4)
Sponsor: AbbVie Inc.
PDUFA Goal Date: September 28, 2021

Materials Reviewed:

Abuse-related preclinical and clinical data in NDA submission
Prior CSS reviews by:

- C. Reissig (9/9/2020)
- K. Bonson (4/16/2019)
- K. Bonson (4/14/2018)
- K. Bonson (6/15/2017)

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Neurology Products 2 (DN2) to evaluate the abuse potential of atogepant (Qulipta, NDA 215206). The drug product is indicated for the preventive treatment of migraine in adults with < 15 migraine days per month. The recommended dose is 30 or 60 mg daily in subjects without renal impairment. CSS has previously reviewed this drug under IND multiple times to guide the Sponsor's abuse potential assessment program.

Atogepant is a new molecular entity (NME). According to the Sponsor, atogepant (previously known as MK-8031) is an orally active, selective, calcitonin gene-related peptide (CGRP) receptor antagonist. Other CGRP antagonists have previously been tested for the treatment of migraine, either acutely or prophylactically with ubrogepant receiving FDA approval on December 23rd, 2019. Ubrogepant is not scheduled under the Controlled Substances Act (CSA) and does not appear to have an abuse potential.

2. Conclusions

- Based on the receptor binding studies, preclinical data, and the profile of abuse-related AEs observed in clinical studies, atogepant does not appear to present a signal for abuse.

- Based on data from clinical discontinuation studies, atogepant does not appear to produce physical dependence and/or withdrawal.

3. Recommendations

- Atogepant does not appear to present a signal for abuse and does not require scheduling under the Controlled Substances Act (CSA).

- Because atogepant will not be scheduled under the CSA and does not present a potential for abuse, Section 9 should not be included in the label.

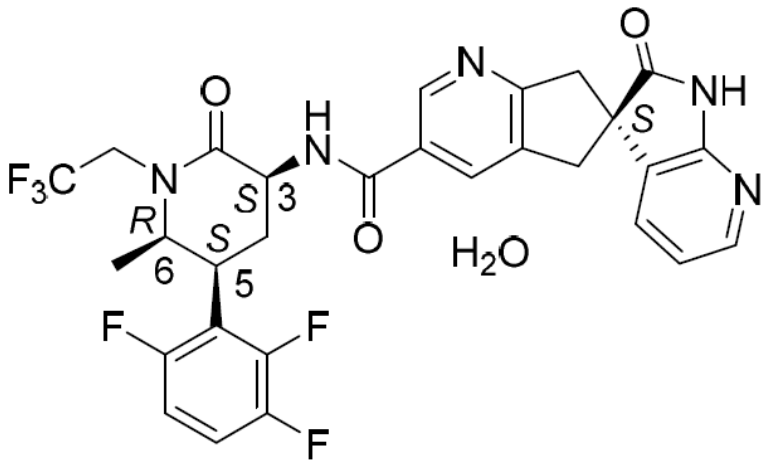
II. DISCUSSION

1. Chemistry

Atogepant does not appear to be structurally similar to approved opioid drugs or other drugs with abuse potential. It has poor water solubility making abuse by injection difficult. Synthesis of atogepant involves a complex process that would not be feasible for illicit synthesis.

The molecular formula (b) (4) The CAS number for atogepant is 1374248-81-3. The chemical (IUPAC) name for atogepant is: (S)-*N*-((3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-

trifluorophenyl)piperidin-3-yl)-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[b]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide. The chemical structure of atogepant monohydrate appears below:



2. Nonclinical Pharmacology

The Sponsor performed studies in rodents to assess the CNS effects of atogepant (CNS/modified Irwin study TT#11-5500), physical dependence and withdrawal (study CGP-PH-07), and a self a-administration study (CGP-PH-08). The data from these studies are described below.

CNS effects (study TT#11-5500)

In the CNS/modified Irwin study, the Sponsor examined orally administered atogepant (MK-8031) at doses of 20 and 100 mg/kg in mice. In the study, female mice (n=15) were placed in clear plastic containers for observations and to acclimate to their environment. Mice were removed 0.5, 1.0, and 2.0 hours after dosing. An additional 25 (n=25) mice were dosed for PK assessments. The 40 mice were separated into eight groups of n=5/group. Two groups received vehicle alone, the remaining six groups received a single atogepant dose of either 20 or 200 mg/kg. After dosing, functional observational batteries were performed where the mice were examined for neurological effects and general behaviors. Grip strength and muscle tone were also assessed along with body temperature and pupil diameter. According to the Sponsor, no neurobehavioral findings were observed at any dose and the Sponsor concluded the no-observed-effect-level (NOEL) for neurobehavioral effects after a single oral dose in conscious mice is ≥100 mg/kg of MK-8031.

Self-administration study (CGP-PH-08)

The reinforcing effects of atogepant were evaluated using a self-administration procedure in heroin-maintained rats. In the self-administration study, male Sprague Dawley rats were initially trained to lever-press for food and subsequently trained to self-administer a low dose of heroin (0.015 mg/kg/injection, i.v.) on a FR5 schedule of reinforcement. Saline (0.5 mL/kg/injection, i.v.) was used as a control. Atogepant doses of 0.003, 0.01, 0.03 and 0.1 mg/kg/injection were evaluated for their ability maintain reinforcement.

According to the Sponsor, heroin (0.015 mg/kg/injection, i.v.) consistently maintained high levels of self-administration (18.2±0.7 injections/session [mean of the last 3 test sessions], n=19), while saline (i.v.) maintained low rates of self-administration (4.7±0.3 injections/session, n=19). The mean number

of injections of atogepant (0.003, 0.01, 0.03 and 0.1 mg/kg/injection) were 5.8±1.0, 5.6±1.2, 5.0±1.4, and 6.8±0.8 injections/session, respectively (n=7-9). The Sponsor concluded that none of the doses of atogepant were reinforcing, a finding consistent with the data and low rates of self-administration of atogepant.

Physical Dependence and Withdrawal (study CGP-PH-07)
A physical dependence study was performed in male Sprague Dawley rats. In the study, behavioral, physical, and physiological signs were assessed during repeated (28 day) twice daily (b.i.d.) oral dosing of atogepant to male Sprague Dawley rats. Atogepant was tested at (10 and 30 mg/kg p.o. b.i.d.). The Sponsor asserts that these doses produced Cmax values equivalent to, and 5 times higher than the highest therapeutic dose. The Sponsor notes that the high dose of atogepant (30 mg/kg p.o. b.i.d.) produced significant decreases in body weight during the first week of dosing. The lower dose of atogepant (10 mg/kg p.o. b.i.d.) produced subdued behavior and decreased locomotor activity on Days 1 and 2 of week 1, and erratic respiration on Day 2 only. Piloerection was observed on several days throughout the on-dose phase, and was statistically significant on Weeks 1-3. A similar profile was observed at the higher dose of atogepant, though the effects were smaller in magnitude with no clear dose-response relationship. The Sponsor concluded that during the withdrawal phase, body weight, food and water intake and body temperature of the atogepant (10 and 30 mg/kg p.o. b.i.d.) treated rats did not differ from those of the vehicle-treated group. Upon cessation of atogepant administration, no new behaviors or physical signs were reported during the withdrawal phase.

In contrast, according to the Sponsor, repeat dosing of the positive control, morphine (30 mg/kg p.o. b.i.d), was associated with changes in body weight, food and water intake, and clinical signs consistent with the development of tolerance. When dosing was withheld, symptoms of withdrawal, and physical dependence emerged. The Sponsor asserts that these data suggest that atogepant did not produce withdrawal signs indicative of physical dependence. We agree with the Sponsor's interpretation of these study results.

2.1 Receptor Binding and Functional Assays

Atogepant exhibited high affinity for the human CGRP receptors (Ki = 15-26 pM). In off target and in vitro binding screens, atogepant did not exhibit significant affinity for CNS targets known to be associated with drugs of abuse, including dopamine, cannabinoid, acetylcholine, opioid, GABA, or NMDA receptors, and transporters for serotonin and norepinephrine. The concentration of atogepant used in this binding study was ~10X greater than the Cmax at the highest human dose of 60 mg. These data suggest minimal off target effects and a mechanism of action similar to rimegepant and ubrogepant, drugs that are not scheduled under the CSA and considered to have a low potential for abuse.

3. Clinical Pharmacology

According to the Sponsor, atogepant is moderately plasma protein bound in humans (~95%) which may limit entry into the CNS. Atogepant produced a Tmax of 1-2 hours after oral administration, with a Cmax of about 740 ng/mL and an AUC of 3470 ng*h/mL after a 60 mg dose. Atogepant is described by the Sponsor as approximately dose-proportionate pharmacokinetics from 1-300 mg. The terminal elimination half-life is about 11 hours and little drug accumulated after repeated dosing.

4.2 Adverse Event Profile Through all Phases of Development

Based on CSS input, the Sponsor collected and summarized abuse-related AEs. The following terms were used in the analysis:

Euphoria-related terms	Terms indicative of impaired attention, cognition, mood, and psychomotor events	Dissociative/Psychotic terms
Dizziness	Somnolence	Psychotic disorder
Euphoric mood	Affective disorder	Aggression
Feeling abnormal	Mood altered	Confusional state
Feeling drunk	Drug tolerance	Disorientation
Feeling of relaxation	Drug withdrawal syndrome	
Inappropriate affect	Substance abuse	
Thinking abnormal	Substance dependence	
Hallucination	Substance use	
	Substance-induced mood disorder	
	Substance-induced psychotic disorder	
	Disturbance in attention	

According to the Sponsor, when examining abuse-related AEs from pivotal, placebo-controlled studies, TEAEs predictive of abuse potential were reported by 1.5% of participants in the placebo group versus 3.3% to 4.8% of participants in the atogepant treated groups. The most commonly observed abuse-related AEs were dizziness and somnolence, but these did not occur in conjunction with other abuse-related AEs (e.g., euphoria). In addition, the incidence of abuse-related AEs did not appear to be dose-related. The AEs from these studies appear below and were taken from ISS table 7-1.7.1

Category Preferred Term	Placebo (N=408) n (%)	Atogepant 10 mg QD (N=314) n (%)	Atogepant 30 mg QD (N=411) n (%)	Atogepant 60 mg QD (N=417) n (%)	Atogepant 30 mg BID (N=86) n (%)	Atogepant 60 mg BID (N=91) n (%)
Abuse-related TEAE	**6 (1.5)**	**15 (4.8)**	**16 (3.9)**	**17 (4.1)**	**3 (3.5)**	**3 (3.3)**
Somnolence	4 (1.0)	9 (2.9)	8 (1.9)	10 (2.4)	1 (1.2)	0
Dizziness	2 (0.5)	5 (1.6)	8 (1.9)	6 (1.4)	1 (1.2)	3 (3.3)
Disturbance in attention	0	2 (0.6)	0	1 (0.2)	1 (1.2)	0
Feeling abnormal	0	1 (0.3)	0	0	0	0

MedDRA Version 22.0 was used to code adverse events.
Based on Group 1 Studies (CGP-MD-01 and 3101-301-002).
N = number of participants in the Safety Population of the treatment group. n = number of participants within the specific category. Percentages calculated as 100 × (n/N).
Participants are counted only once within each preferred term.
Source: Module 5.3.5.3, ISS Table 7-1.7.1

Abuse-related AEs were also summarized from the two long term safety studies that were 40 and 52 weeks in duration, respectively. In the long-term safety studies, abuse-related AEs were observed infrequently. According to the Sponsor, abuse-related AEs were reported for 15.3% of subjects in the standard of care (SOC) group and only 3.4% of participants in the atogepant group. Similar to the placebo-controlled studies, the most commonly observed abuse-related AEs were dizziness and somnolence. Two of events of "feeling abnormal" were reported and subjects used the verbatim terms "brain fog" and "mental fog." There was one occurrence of "feeling drunk" that a subject described as a combination of disorientation, vertigo, and light-headedness. No events of euphoria were reported in the

pooled, longer term studies. The abuse-related AEs for these studies appear below from ISS table 7-2.7.1

Category Preferred Term	Standard of Care (N=196) n (%)	Atogepant 60 mg QD (N=1198) n (%)
Participants with abuse-related TEAEs	**30 (15.3)**	**41 (3.4)**
Dizziness	22 (11.2)	27 (2.3)
Somnolence	8 (4.1)	10 (0.8)
Disturbance in attention	1 (0.5)	3 (0.3)
Feeling abnormal	0	2 (0.2)
Feeling drunk	0	1 (0.1)
Mood altered	1 (0.5)	0

MedDRA Version 22.0 was used to code adverse events.
Based on Group 2 Studies (3101-302-002 and 3101-309-002 with the interim data cut as of 25 May 2020).
N = number of participants in the Safety Population of the treatment group. n = number of participants within the specific category. Percentages calculated as 100 × (n/N).
Participants are counted only once within each preferred term.
Source: Module 5.3.5.3, ISS Table 7-2.7.1

Finally, the Sponsored pooled their phase 1 studies to examine abuse-related AEs. Similar to the other pooled study groups, dizziness and somnolence were the most commonly reported abuse-related AEs, reported at a maximum incidence of 5.5%. A single event of feeling abnormal and disturbance in attention was also reported. The pooled, phase 1 abuse-related AEs appear below from ISS table 7-4.7.1

Category Preferred Term	Placebo (N=132) n (%)	Atogepant < 10 mg QD (N=31) n (%)	Atogepant 10 to 20 mg QD (N=35) n (%)	Atogepant 30 mg QD (N=23) n (%)	Atogepant 40 to 50 mg QD (N=42) n (%)	Atogepant 60 mg QD (N=285) n (%)	Atogepant > 60 mg QD (N=109) n (%)	Atogepant 30 or 60 mg BID (N=22) n (%)
Abuse-Related TEAE	**2 (1.5)**	**1 (3.2)**	**0**	**1 (4.3)**	**1 (2.4)**	**9 (3.2)**	**8 (7.3)**	**1 (4.5)**
Dizziness	2 (1.5)	1 (3.2)	0	1 (4.3)	1 (2.4)	6 (2.1)	6 (5.5)	1 (4.5)
Disturbance in attention	0	0	0	0	0	0	1 (0.9)	0
Feeling abnormal	0	0	0	0	0	0	1 (0.9)	0
Somnolence	0	0	0	0	0	3 (1.1)	1 (0.9)	0
Disorientation	1 (0.8)	0	0	0	0	0	0	0

MedDRA Version 22.0 was used to code adverse events.
Based on Group 4 Phase 1 Studies (CGP-PK-01, CGP-PK-02, CGP-PK-03, CGP-PK-04 Part A, CGP-PK-04 Part B, CGP-PK-06, CGP-PK-12, CGP-PK-13, 3101-101-002, 3101-102-002, 3101-103-002, MK-8031-001 Part 1, MK-8031-001 Part 2, MK-8031-002 Part 1, MK-8031-002 Part 2, MK-8031-003, MK-8031-004, MK-8031-005, MK-8031-008).
N = number of participants within the treatment group in the Safety Population.
n = number of participants within a specific category. Percentages are calculated as 100 × (n/N).
Participants are counted only once within each category and preferred term.
Source: Module 5.3.5.3, ISS Table 7-4.7.1

We conclude that these AE data are consistent with atogepant as a drug that does not produce a signal of abuse potential.

4.5 Tolerance and Physical Dependence Studies in Humans

According to the Sponsor, neither the preclinical nor clinical data suggest the development of physical dependence. In the clinical program, no AEs of “drug tolerance” or “drug withdrawal syndrome” were

reported. Finally, in the pivotal placebo-controlled studies, no newly emergent AEs were reported after drug discontinuation. The Sponsor interpreted these data to suggest the absence of a rebound following drug discontinuation. We agree with the Sponsor's conclusions concerning physical dependence and rebound.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHAD REISSIG
07/17/2021 05:30:26 PM

DOMINIC CHIAPPERINO
07/18/2021 09:37:39 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 16, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215206
Product Name and Strength:	Atogepant tablet, 10 mg, 30 mg, 60 mg
Applicant/Sponsor Name:	AbbVie Inc.
OSE RCM #:	2021-211-1
DMEPA 2 Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA 2 Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

AbbVie Inc. submitted revised container labels and carton labeling received on May 25, 2021 for atogepant tablets. The Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 ASSESSMENT

We note, AbbVie proposes a new packaging configuration for professional samples. Instead of (b) (4) AbbVie proposes a professional sample packaging configuration of a 4-count carton containing a blister foil card, only. We do not object to this change in proposed packaging configuration from a medication error perspective.

3 CONCLUSION

The revised container labels and carton labeling is unacceptable from a medication error perspective. The prominence of the strength statement on the container labels and carton

[a] Morris, C. Label and Labeling Review for atogepant (NDA 215206). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 15. RCM No.: 2021-211.

labeling can be improved to reduce the risk of numerical confusion between the strength and net quantity.

4 RECOMMENDATIONS FOR ABBVIE INC.

We recommend the following be implemented prior to approval of this NDA:

Table 1. Identified Issues and Recommendations for AbbVie Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
	The proposed proprietary name, (b) (4) was withdrawn on 6/21/21.	Review of the proposed proprietary name, Qulipta, is currently under review.	Denote the proprietary name placeholder as "Tradename" until a proprietary name has been granted conditional approval. We recommend you present "Tradename" in your intended design.
Container Labels			
	The strength is located at the bottom of the principal display panel (PDP), below the net quantity statement, and could be misinterpreted for the net quantity.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	We recommend you increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6) by repositioning it to the center of the PDP, and relocate the net quantity statement to the bottom of the PDP.

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
07/16/2021 11:00:35 AM

CELESTE A KARPOW
07/16/2021 11:17:08 AM

Clinical Inspection Summary

Date	06/07/2021
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Daniel Ngembus, Regulatory Project Manager Viveca Livezey, M.D., Medical Officer Heather Fitter, M.D., Team Leader Division of Neurology 2 Office of Neuroscience
NDA #	215206
Applicant	AbbVie Inc.
Drug	Atogepant
NME	Yes
Proposed Indication	Preventive treatment of migraine in adults with <15 migraine days per month
Consultation Request Date	3/5/2021
Summary Goal Date	6/25/2021
Priority/Standard Review	Priority
Action Goal Date	9/28/2021
PDUFA Date	9/28/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Kroll, McConnehey, Helm, and Hemphill were inspected in support of this NDA, covering Protocols CGP-MD-01 and 3101-301-002. Despite some protocol deviations noted at the sites of Drs. Kroll and McConnehey, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

II. BACKGROUND

Atogepant oral tablets are being developed under NDA 215206 (IND 114780) for the preventive treatment of migraine in adults with <15 migraine days per month. The sponsor has submitted a Phase 2/3 study (CGP-MD-01) and a Phase 3 study (3101-301-002) to support the safety and efficacy of atogepant in the preventive treatment of migraine.

Protocol CGP-MD-01

Title: "A Phase 2/3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of multiple dosing regimens of oral AGN-241689 in episodic migraine prevention"

Subjects: 825 enrolled

Sites: 78 sites in the United States

Study Initiation and Completion Dates: 9/6/2016 to 4/23/2018

This was a randomized, double-blind, placebo-controlled, parallel-group study. Included were males or females, 18 to 75 years of age (inclusive), with the following migraine criteria:

- At least a 1-year history of migraine with or without aura per International Classification of Headache Disorders (ICHD) criteria
- Less than 50 years of age at time of migraine onset
- History of 4 to 14 migraine/probable migraine headache days per month in the 3 months prior to Visit 1

Excluded were subjects with a current diagnosis of chronic migraine, ≥15 headache days per month in the 3 months prior to Visit 1, or history of an inadequate response to 3 or more medications prescribed for prevention of migraine.

The study was comprised of three periods:

Baseline/Screening Period (28 days)
Subjects recorded migraine information daily in an electronic diary. Subjects were required to have 4 to 14 migraine/probable migraine headache days during this 28-day baseline period to be eligible for randomization into the double-blind treatment period.

A ***migraine headache day*** was defined as any day on which a headache met ***all*** of the following criteria:

1. Headache had at least *two* of the following four characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravated by or causing avoidance of routine physical activity
2. At least *one* of the following: nausea and/or vomiting, photophobia and phonophobia, typical aura accompanying or within 60 minutes before the headache begins
3. Duration of headache lasting ≥2 hours on a calendar day unless an acute, migraine-specific medication (e.g., triptan, ergot derivative) was used after the start of the headache, in which case no minimum duration was specified

A ***probable migraine headache day*** was defined as meeting one criterion from (1) above and at least one criterion from (2) above ***or*** two criteria from (1) and no criteria from (2). Criterion (3) still needed to be met for both.

Subjects with ≥15 headache days during this 28-day baseline were excluded from the study. A headache day was defined as a day on which headache pain lasted ≥2 hours unless an acute headache medication (e.g., ibuprofen, triptan) was used after the start of the headache, in which case no minimum duration was specified.

Double-Blind Treatment Period (12 weeks)
Subjects were randomized (1:2:1:2:1:2) to one of 6 treatment groups:

- Atogepant 10 mg QD
- Atogepant 30 mg QD
- Atogepant 30 mg BID
- Atogepant 60 mg QD
- Atogepant 60 mg BID
- Placebo

Subjects recorded migraine information daily in the electronic diary.

Safety Follow-up Period
A safety follow-up visit occurred 4 weeks after the end of the double-blind treatment period.

The *primary efficacy endpoint* was the change from baseline in mean monthly migraine/probable migraine headache days across the 12-week treatment period.

Protocol 3101-301-002

Title: "A Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and tolerability of oral atogepant for the prevention of migraine in participants with episodic migraine (ADVANCE)"

Subjects: 902 enrolled

Sites: 128 sites in the United States

Study Initiation and Completion Dates: 12/14/2018 to 6/19/2020

This was a randomized, double-blind, placebo-controlled, parallel-group study. Inclusion criteria were similar to Protocol CGP-MD-01 with the exception of a broader age range of 18 to 80 years (inclusive) and a history of 4 to 14 migraine days (not including probable migraine days) per month in the 3 months prior to Visit 1.

The study was comprised of three periods:

Baseline/Screening Period (28 days)

Subjects recorded migraine information daily in an electronic diary. Subjects were required to have 4 to 14 migraine headache days during this 28-day baseline period to be eligible for randomization into the double-blind treatment period.

Subjects with ≥15 headache days per month, on average, across the 3 months prior to Visit 1 were excluded. Subjects with ≥15 headache days in the 28-day baseline period were also excluded from the study.

Double-Blind Treatment Period (12 weeks)
Subjects were randomized (1:1:1:1) to one of 4 treatment groups:

- Atogepant 10 mg QD
- Atogepant 30 mg QD
- Atogepant 60 mg QD
- Placebo

Randomization was stratified based on prior exposure (yes/no) to at least one prior migraine prevention medication with proven efficacy. Subjects recorded migraine information daily in the electronic diary.

Safety Follow-up Period
A safety follow-up visit will occur 4 weeks after the end of the double-blind treatment period.

The *primary efficacy endpoint* was the change from baseline in mean monthly migraine headache days across the 12-week treatment period.

Rationale for Site Selection

The clinical investigators inspected for Protocol CGP-MD-01 were selected primarily based on the impact of the site on the primary efficacy endpoint analysis. The clinical investigators inspected for Protocol 3101-301-002 were selected primarily based on risk ranking in the site selection tool as well as prior inspectional history.

III. RESULTS

1. Robin Kroll, M.D.
Site #181
Seattle Women's Health, Research, Gynecology
3216 NE 45th Place, Suite 100
Seattle, WA 98105
Inspection Dates: 4/19/2021 – 4/23/2021

At this site for Protocol CGP-MD-01, 28 subjects were screened, 17 were randomized, and 13 subjects completed the study. Three subjects discontinued the study due to withdrawal of consent. Subject # (b) (6), randomized to atogepant 60 mg BID, discontinued due to the adverse events of dizziness, fatigue, affect lability.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine/probable migraine days).

The primary efficacy endpoint data, migraine/probable migraine days, were entered by subjects into an electronic diary (eDiary). The eDiary vendor, CRF Health, provided a CD to the site containing all eDiary data entries and audit trails. This data was verified against the sponsor data listings. No discrepancies were identified.

The inspection noted the following findings:

- Incorrect investigational product (IP) was dispensed to one of 17 (5.6%) enrolled subjects. At Visit 6 (Week 1), Kit #115933 (atogepant 60 mg BID) was dispensed to Subject # (b) (6) instead of the correct Kit #111593 (atogepant 30 mg BID). This subject self-administered the incorrect IP during this week. No other dosing errors were made for this subject. No adverse events were noted in the sponsor data line listings during the dates that the subject received the wrong IP. According to the clinical investigator, the site did not realize the error until a subsequent visit (Visit 7, ~4 weeks later), and the error was then reported to the sponsor and IRB.

- Four unreported adverse events occurred in one of 17 (5.9%) subjects enrolled. During the safety follow-up period, Subject # (b) (6) experienced a fall with a resulting ulna fracture, both of which were reported as adverse events. The subject was seen by a physician not affiliated with the study for wrist pain secondary to the fall. The clinical investigator obtained the medical records for

that visit. In the review of systems section of the medical record, the treating physician noted complaints of nausea, loss of appetite, fever, and chills, which were not reported by the clinical investigator as adverse events. This subject was randomized to atogepant 30 mg QD, and received the last dose on (b) (6) The fall and fracture occurred on (b) (6), two days after receiving the last dose of atogepant. There is no further information regarding when these adverse events began, the severity of the symptoms, or the resolution.

- One unreported concomitant medication in one of 17 (5.9%) subjects enrolled. Subject # (b) (6) took acyclovir 800 mg QD from (b) (6) and acyclovir 800 mg BID from (b) (6) for oral herpes. The acyclovir was recorded on a paper log but was not entered into the eCRF and therefore not reported to the sponsor. Per protocol, acyclovir was not a prohibited concomitant medication. The adverse event (oral herpes) was reported. This subject, randomized to placebo, withdrew consent before completing the double-blind treatment period.

Reviewer's comment: The investigational product dispensing error resulted in a subject receiving the incorrect dose of atogepant for one week during Visit 6. However, since this subject was randomized to atogepant 30 mg BID, a dose for which the sponsor is not seeking approval, this error would not impact the overall efficacy analyses. This subject did not experience adverse events during the time the higher dose was administered.

No further information was available regarding the adverse events that were noted in the subject who was evaluated by an outside physician for an ulna fracture. This subject did complete the safety follow-up visit on (b) (6), and the subject did not complain of any of the four unreported (non-SAE) adverse events at that time.

2. Brock McConnehey, D.O.
Site #235
Northwest Clinical Trials
888 North Cole Road
Boise, ID 83704
Inspection Dates: 3/29/2021 to 4/2/2021

At this site for Protocol CGP-MD-01, 52 subjects were screened, 25 were randomized, and 23 subjects completed the study. Two subjects discontinued the study due to withdrawal of consent (one moving out of town, the other could no longer comply with the time commitments of study).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring

documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine/probable migraine days).

The primary efficacy endpoint data, migraine/probable migraine days, was entered by subjects into an electronic diary (eDiary). The eDiary vendor, CRF Health, provided a CD to the site containing all eDiary data entries and audit trails. This data was verified against the sponsor data line listings. No discrepancies were identified.

The inspection noted the following findings:

- One of 25 (4%) subjects enrolled did not meet eligibility criteria. Subject # (b) (6) began taking sertraline 50 mg QD for anxiety on (b) (6) between the screening and baseline visits. Per protocol, concomitant SSRIs were only permitted if the dose was stable for at least 60 days prior to screening Visit 1. This subject was randomized to atogepant 30 mg QD.

- One unreported adverse event occurred in one of 25 (4%) randomized subjects. According to progress notes on (b) (6), Subject # (b) (6) reported nausea starting on (b) (6) (during the double-blind treatment period). Nausea was not reported in the eDiary from (b) (6), and headache occurred on only one of those days. No further information was available. This subject was randomized to atogepant 60 mg BID.

- Four unreported concomitant medications occurred in four of 25 (16%) randomized subjects:
    - Subject # (b) (6) took one dose of hydrocodone/acetaminophen (Vicodin) for sacral pain on (b) (6), during the double-blind treatment period. This subject was randomized to atogepant 60 mg BID. Per protocol, acetaminophen and opioids were allowed for the acute treatment of migraine. The protocol does not mention use of these concomitant medications for other pain conditions.

    - Subject # (b) (6) took oxycodone/acetaminophen (Percocet) for kidney stone pain on (b) (6) during the double-blind treatment period. This subject was randomized to atogepant 60 mg QD. Per protocol, acetaminophen and opioids were allowed for the acute treatment of migraine. The protocol does not mention use of these concomitant medications for other pain conditions.

    - Subject # (b) (6) began bupropion on (b) (6), during the safety follow-up period, for worsening of anxiety/depression. This subject was randomized

to placebo, with the last dose administered on (b) (6) Bupropion was not a prohibited medication. No efficacy data was collected during the safety follow-up period.

- Subject # (b) (6) began fluoxetine on (b) (6), during the safety follow-up period, for anxiety. This subject was randomized to atogepant 10 mg QD, with the last dose administered on (b) (6). Fluoxetine was an allowable concomitant medication only if the subject was on a stable dose for at least 60 days prior to Visit 1; therefore, this unreported concomitant medication was also an unreported protocol deviation. No efficacy data was collected during the safety follow-up period.

Reviewer comments: The inspection noted an unreported adverse event and four unreported concomitant medications. Two of the unreported concomitant medications were pain medications taken for 1 to 3 days for nonmigraine pain. Only one of these subjects was randomized to a dose for which the sponsor is seeking approval (60 mg QD). It is unlikely that administration of pain medication for 3 days in this subject would impact the primary efficacy analysis of change in mean monthly migraine days across the 12-week treatment period. The other two unreported concomitant medications were taken by subjects during the safety follow-up period (and not the treatment period), when no efficacy data was selected.

One subject (# (b) (6) who did not meet eligibility criteria was enrolled and randomized to atogepant 30 mg QD, a dose for which the sponsor is seeking approval. This subject began taking sertraline after the screening visit and throughout the study. It should be noted that there is little evidence that SSRIs, such as sertraline, are effective for the prevention of migraine. It is unlikely that this single ineligible subject had any significant impact on the efficacy results of the study.

3. Melvin Helm, M.D.
Site #228
California Headache and Balance Center
1865 E. Alluvial Ave., Suite 102
Fresno, CA 93720
Inspection Dates: 4/21/2021 – 4/27/2021

At this site for Protocol 3101-301-002, 23 subjects were screened, 15 were randomized, and 14 subjects completed the study. Subject (b) (6), randomized to atogepant 60 mg QD, discontinued the study 5 days after randomization due to the adverse events fatigue and ear pain

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring

documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine days).

The primary efficacy endpoint data, migraine days, was entered by subjects into an electronic diary (eDiary). The eDiary vendor, (b) (4), provided a USB to the site containing all eDiary data entries. This data was verified against the sponsor data line listings. No discrepancies were identified. There was no evidence of underreporting of adverse events or concomitant medications.

4. John Michael Hemphill, M.D.
Site #524
Meridian Clinical Research
6602 Waters Avenue, Bldg C
Savannah, GA 31406
Inspection Dates: 5/4/2021 – 5/6/2021

At this site for Protocol 3101-301-002, 31 subjects were screened, 25 were randomized, and 23 subjects completed the study. Two subjects discontinued the study due to loss to follow-up and withdrawal of consent.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (migraine days).

The primary efficacy endpoint data, migraine days, was entered by subjects in an electronic diary (eDiary). The eDiary vendor, (b) (4) provided a USB to the site containing all eDiary data entries. This data was verified against the sponsor data line listings. No discrepancies were identified. There was no evidence of underreporting of adverse events or concomitant medications.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Division Director (Acting) and
Branch Chief/Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/NDA #215206
Division of Neurology 2/Division Director/Nicholas Kozauer
Division of Neurology 2/Medical Team Leader/Heather Fitter
Division of Neurology 2/Medical Officer/Viveca Livezey
Division of Neurology 2/Project Manager/Daniel Ngembus
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director (acting) and GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARA L ALFARO
06/07/2021 09:00:09 AM

PHILLIP D KRONSTEIN
06/07/2021 09:03:34 AM

KASSA AYALEW
06/07/2021 09:05:16 AM

Tracked Safety Issue (TSI) Integrated Review Memorandum

Division of Hepatology and Nutrition (DHN)
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Adminstration

NDA	*215206*
Drug name	Atogepant
Safety Issue Name	*Drug-induce liver injury* *120 Day Safety Report*
Author name	Paul H. Hayashi, MD, MPH
Date	*May 29, 2021*

I. OVERALL ASSESSMENT AND RECOMMENDATION(S)

DHN DILI Team is already consulting on liver injury risk for this NDA. We had not seen a significant liver toxicity potential that threatened approval of this drug. However, our assessment and recommendations may be affected by the review of this 120 Day Safety report. The report has 5 new cases from studies outside the NDA's ISS Group 1 and 2. We reviewed all 5 cases. There were no Hy's Law cases, but the reports raise a concern that Japanese or Asians, in general, may be at increased risk of liver injury. The DILI Team met with the medical officer for the Division of Neurology 2 (DN2) on Jun 1, 2021. We will send an information request for clarification of this issue.

II. BACKGROUND

Atogepant (AGPT) is an oral small molecule antagonist of the calcitonin gene related peptide (CGRP) receptor. It is under NDA review for the prevention of migraine headaches in adults with more than 15 migraine days per month. Other agents in this class have had problems with drug-induced liver injury (DILI). The DILI Team was asked by the DN2 on Feb 18, 2021 to review "patients with abnormal LFTs for potential liver toxicity". We were asked to give opinion on whether Atogepant "carries a risk of potential liver toxicity and, if so, how this may inform labeling." Since sending our consult to DN2, May 15, 2021, the sponsor sent a 120-Day Safety Update report (Seq 17, SDN 17) on May 19, 2021. We held up finalizing our consult into DARRTs to review this report.

III. SIGNIFICANT REVIEW FINDINGS

The Safety Report has two areas of interest: (1) Updated data for the ISS Group 2 and (2) New cases of liver enzyme elevations in 2 studies outside the ISS Groups.

ISS Group 2 OLE Studies: Updated eDISH plot did not identify any cases in Hy's Law quadrant. Proportions of patients with transaminases over 3x ULN and higher were not significantly changed from earlier data submitted with the NDA. Just 1 new case ([redacted] (b) (6), Study 3101-309-002) required review with AST elevation over 3x ULN. We reviewed the case narrative and graphic. This was not DILI. AST elevation occurred 324 days after AGPT start (60 mg/d). The rise was concurrent with increased physical activity and CPK of 4806 U/L. ALT was 38 U/L and bilirubin 0.2 mg/dL. Patient also reported recent increase in alcohol intake. CPK and AST fell to normal within 30 days. AGPT was continued without dose change.

Cases from Studies Not Included in Group 2 OLE Studies: The report describes 5 new case of liver enzyme elevations. No cases met Hy's Law liver test elevation criteria. No case developed jaundice. All recovered.

a. Study CGP-PK-14 (Phase 1 study of PK in health volunteers, IND 114780, Sq 172, 5.3.3.4): One patient of black race had elevation in ALT and AST more that 3x ULN after taking AGPT, 60 mg/d, for 7 days. This case's narrative and graphic data were reviewed and assessed as probable DILI due to AGPT. However, this reviewer could not find overall study safety data. Target enrollment is 50 healthy volunteers of which 25 would get AGPT at varying doses.
b. Study 3101-306-002 (OLE of Phase 3 RCT, 3101-303-002, IND 114870, Seq 172, 5.3.5.1). Four cases developed elevation in ALT and/or AST greater than 3x ULN. All four were Japanese. We assessed 2 as probable DILI due to AGPT, 1 possible and 1 unlikely. An independent Causality Assessment Committee (CAC) assessed them as 3 probable and 1 unlikely, while the sponsor's internal review assessed them as 3 possible and 1 unlikely. Target enrollment for this Phase 3, RCT was 750, randomized 2:1, AGPT to placebo, but this reviewer could not find summary safety information, current enrollment or demographics for the OLE. The sponsor did not provide proportions of patients with elevation in transaminases by race. We are unclear whether study 3101-306-002 was restricted to Japanese only nor total number of Japanese enrolled.
c. Summary of 5 new cases from CGP-PK-14 and 3101-303-002:

ID	Study	Causality Score	Alternate diagnosis	Age (y)	Sex	Race	Hy's Law	Latency from start drug	Latency from stop drug	Symptoms	Latency symptoms (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)	Washout 50% ALT (da)	Washout ALT normal (da)
(b) (6)	CGP-PK-14	3		30	M	Black	No	6	-1	No		234	154	104	0.7	6.88	4.53	42	NA
	3101-306-002	3		49	F	Asian	No	112	-24	No		309	184	104	0.9	9.09	5.41	26	68
	3101-306-002	3		49	F	Asian	No	141	-31	No		395	265	116	0.5	10.42	6.99	16	37
	3101-306-002	4	Azithromycin liver injury	42	F	Asian	No	193	-39	Yes	-39	238	109	104	0.6	7.00	3.21	23	NA
	3101-306-002	5	Gallstone disease	51	F	Asian	No	91	-1	Yes	1	594	1094	751	1.9	2.42	4.46	7	14

NA = not available

3 = probable DILI, 4 = possible DILI, 5 = Unlikely DILI

d. Japanese Subgroup Analyses: Because 4 of the new cases were Japanese, the sponsor examined AGPT concentrations by race/nationality (white, black, Asian, Japanese and American Indian). They did not see higher levels that might be explanatory (see Figures 10 and 11). However, we found no summary data of proportions of patients with liver enzyme elevations by Japanese versus other races in study 3101-303-002 or other studies.

Because the sponsor is hoping to market AGPT in Japan, a Phase 1, RCT specifically looking at PK in Japanese versus Caucasians was done in 2017 (Study 3101-101-002, Sq 18, 5.3.3.3). 40 Japanese and 10 Caucasians enrolled. The Japanese were randomized 4:1 to varying exposures of AGPT and placebo. There were no cases of transaminase elevations above 3x ULN in any patient, Japanese or Caucasian (Clinical Study Report, page 251).

IV. CONCLUSIONS

The report raises questions about an increased DILI risk in Japanese, or Asians overall. From the data given, it appears that the proportion of patients with elevation in transaminases is higher in Japanese compared to other races in a Phase 3 study, which is not included in the ISS Group 1 or 2 of the NDA. Enrollment status and race demographics are unclear in this Phase 3 study. Precise proportions of patients with elevated transaminases by race are not provided.

V. RECOMMENDED REGULATORY ACTION(S)

The DILI Team is already consulting on liver injury risk for this NDA. After discussion with DN2, we will request liver test abnormalities by race in the ISS, Study 3101-303-002 and Study 3101-0306-002. We will request enrollment status by race in study 3101-306-002.

Paul H. Hayashi -S

Digitally signed by Paul H. Hayashi -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002877340, cn=Paul H. Hayashi -S
Date: 2021.06.02 10:57:22 -04'00'

Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL H HAYASHI
06/02/2021 11:05:50 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 15, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 215206
Product Name and Strength:	atogepant tablet, 10 mg, 30 mg, 60 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AbbVie Inc.
FDA Received Date:	January 28, 2021
OSE RCM #:	2021-211
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

As part of the approval process for atogepant tablet, the Division of Neurology 2 (DN 2) requested that we review the proposed Prescribing Information (PI), Patient Information (PPI), carton labeling and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted PI, container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

The following table (Table 2) outlines issues and recommendations for the Division:

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	Table 1 does not contain a unit of measure after each numeral.	These symbols may be mistaken as opposite of intended.	Add the unit of measure “mg” to each numeral in the recommended dose column.

The following table (Table 3) outlines issues and recommendations to convey to the Applicant:

Table 3. Identified Issues and Recommendations for AbbVie Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The format for the month portion of the expiration date is unclear.	We are unable to assess the month portion of the expiration date.	Identify whether the format for the month portion of the expiration date will be alphabetical or numerical. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. We recommend that a hyphen or a space be used to separate the portions of the expiration date.
2.	The established name lacks prominence commensurate with the proprietary name.	Does not satisfy 21 CFR 201.10(g)(2).	Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
3.	The dosing statement reads (b) (4)	The language is inconsistent with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read

Table 3. Identified Issues and Recommendations for AbbVie Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			"Recommended Dosage: See prescribing information."
4.	(b) (4)		
5.	The NDC product code (middle 4 digits) are sequential.	The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of similar numbers for the middle digits is not an effective differentiating feature (e.g., -7095- for the 10 mg, -7096- for the 30 mg and (b) (4) for the 60 mg).	Revise the product code in the NDC numbers to ensure that the middle 4 digits are not similar between the strengths. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.
Container Labels			
1.	The numbers, 97095, 97096, 97097 appear on the principal display panel (PDP) and it is unclear what these numbers represent.	We are concerned these numbers clutter the PDP and detract from other critical information on the principal display panel.	Clarify whether this information will be dropped before processing and printing or provide justification for their inclusion on the PDP.
2.	As currently presented on the commercial container labels, the	Since the drug barcode is often used as an additional verification in both	We recommend you move the barcode that does not contain the NDC number away from the linear

Table 3. Identified Issues and Recommendations for AbbVie Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	linear barcode, 2D data matrix barcode, and Quick Response Code are located in close proximity.	inpatient and outpatient settings, the presence of multiple barcodes may be confusing to the healthcare providers.	barcode and 2D data matrix barcode, and present it in a size that does not compete with, distract from the presentation of other required or recommended information on the label.
3.	The strength is located at the bottom of the principal display panel, below the net quantity statement, and is less prominent than the "Rx only" and net quantity statements.	From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6) and relocate the net quantity statement away from the product strength. In addition, decrease the prominence of the statement "Rx Only".

4 CONCLUSION

Our evaluation of the proposed atogepant PI, PPI, container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to AbbVie Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for atogepant that AbbVie Inc. submitted on January 28, 2021.

Table 4. Relevant Product Information for atogepant	
Initial Approval Date	N/A
Active Ingredient	atogepant
Indication	For the preventative treatment of migraine in adults with <15 migraine days per month.
Route of Administration	Oral
Dosage Form	Tablet
Strength	10 mg, 30 mg, 60 mg
Dose and Frequency	10 mg, 30 mg, or 60 mg once daily
How Supplied	Sample: (b) (4) Commercial: 30 count bottles
Storage	Store between 20°C and 25°C (68°F and 77°F): excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].
Container Closure[a]	Sample: (b) (4) blister with foil lidding Commercial: HDPE bottle (b) (4)

[a] Retrieved from Lorenz DocuBridge on April 13, 2021

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following atogepant labels and labeling submitted by AbbVie Inc. on January 28, 2021.

- Commercial Container labels
- Professional Sample Container labels
- Professional Sample Carton Labeling
- Professional Sample Blister Foil
- Prescribing Information (Image not shown) available from: \\CDSESUB1\evsprod\nda215206\0001\m1\us\draft-labeling-text.doc
- Patient Information (image not shown) available from: \\CDSESUB1\evsprod\nda215206\0001\m1\us\draft-ppi-text-clean.doc

4 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
04/15/2021 11:29:54 AM

CELESTE A KARPOW
04/15/2021 12:06:30 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 215206
Submission Number	001
Submission Date	1/28/2021
Date Consult Received	2/10/2021
Drug Name	Atogepant
Indication	For the preventive treatment of migraine in adults with <15 migraine days per month.
Therapeutic dose	Atogepant 30 or 60 mg once daily (QD)
Clinical Division	DN2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 2/10/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 11/08/2018 in DARRTS(Link),
- Previous IRT review dated 03/01/2019 in DARRTS(Link) ;
- Investigator's QT study report (SD0001/SDN001; Link); and
- Draft Labeling (SD0001/SDN001; Link)

1 SUMMARY

No significant QTc prolongation effect of atogepant was detected in this QT assessment.

The effect of atogepant was evaluated in a thorough study (CGP-PK-04). The highest dose evaluated was a single dose of 300 mg which covers the high clinical exposure scenario for the 60 mg QD dose (i.e., 2.2-fold Cmax with a strong CYP3A4 inhibitor or OATP inhibitor). The data were analyzed using the by-time analysis as the primary analysis, which did not suggest that atogepant is associated with a significant QTc prolonging effect (refer to section 4.3) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (sections 3.1.2), concentration-QTc analysis (section 4.5), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG parameter	Treatment	Time (Hours)	ΔΔQTCF (msec)	90% CI (msec)
QTc	Atogepant 300 mg	24	1.2	(-1.0, 3.2)
QTc	Moxifloxacin 400 mg	3	10.8	(8.7, 12.9)

For further details on the FDA analysis, please see section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

We agree with the proposed label submitted to SDN 001 (Link).

12.2 Pharmacodynamics Cardiac Electrophysiology At a dose 5 times the maximum (b) (4) recommended dose, TRADENAME does not prolong the QT interval to any clinically relevant extent.
Reviewer's comment: *Geometric mean Cmax in the atogepant treatment is 2,870 ng/mL. According to the sponsor, the typical Cmax after a 60 mg dose is approximately 740 ng/mL (link). Therefore, the study provided 4-fold coverage of the sponsor's reported therapeutic Cmax. On the other hand, the sponsor claims PK linearity at doses up to 300 mg and there is minimal accumulation with the once daily dosing regimen. Therefore, this QT study is expected to provide 5-fold coverage of the highest recommended dose (60 mg QD). Considering variabilities in PK parameters and the flat exposure-response relationship observed in this study, we find it acceptable to report a 5-fold safety margin based on dose.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

The QT-IRT reviewed the QT assessment proposal previously (DARRTS 11/08/2018 (Link) and 03/01/2019 (Link)).

Study CGP-PK-04 is a single oral dose, double-blind, randomized, 3-way crossover, phase I, single-center, placebo- and positive- controlled (moxifloxacin) trial in 60 healthy male and female participants aged 18 through 45 years. The supra-therapeutic dose (300 mg) provided a maximum exposure (C_{max}) greater than the worst-case scenario (i.e. co-administration with itraconazole [CYP3A4/P-gp inhibitor] or rifampicin [OATP inhibitor], 2.2-fold C_{max}) with the highest clinical dose (60 mg QD; no significant accumulation at steady-state irrespective of dose). The primary analysis is by-time point analysis of QTcF.

3.1.2 Nonclinical Safety Pharmacology Assessments

23.9% hERG inhibition at 28 μM. Results from the hERG current evaluation and nonclinical in vivo cardiovascular studies in anesthetized guinea pigs and conscious

rhesus monkeys indicate that atogepant does not significantly affect measures of cardiac conduction or ventricular repolarization.

Reviewer's comment: *Assuming an unbound fraction of 5%, the ratio between hERG IC50 (>28 ug) and free Cmax at the highest tested dose in this study (143.5 ng/mL) is >118-fold. This study provides 4- to 5-fold coverage of the highest therapeutic dose.*

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

Atogepant excluded the 10 msec threshold at the supratherapeutic dose level for ΔΔQTcF.

Reviewer's comment: *Sponsor's analysis results are similar to reviewer's assessment. Please see section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by comparing the moxifloxacin arm and placebo arm at prespecified 2-hour, 3-hour, and 4-hour time points with Hochberg procedure.

Reviewer's comment: *Sponsor's results are consistent with reviewer's estimates. Please see section 4.3.1.1 for more details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline.

Reviewer's comment: *Sponsor's results for QTcF and QTcF change from baseline are similar to reviewer's analysis results. Outlier counts for HR, PR and QRS were not found in sponsor's report body. Please see section 4.4 for more details.*

3.2.3 Exposure-Response Analysis

The sponsor plotted ΔΔQTcF against atogepant concentration. As no trend was noted with increasing atogepant concentration, the sponsor did not conduct additional exposure-response analysis.

Reviewer's comment: *The reviewer conducted linear mixed effect modeling using the pre-specified model in the scientific white paper. Refer to section 4.5 for details of the reviewer's analysis.*

3.2.4 Safety Analysis

No deaths, treatment-emergent SAEs, or AEs leading to discontinuation of study intervention were reported for participants in Part A or Part B, respectively. There were no cardiac related TEAEs.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTc for different treatment groups. The maximum ΔΔQTc values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Time Course (unadjusted CIs).

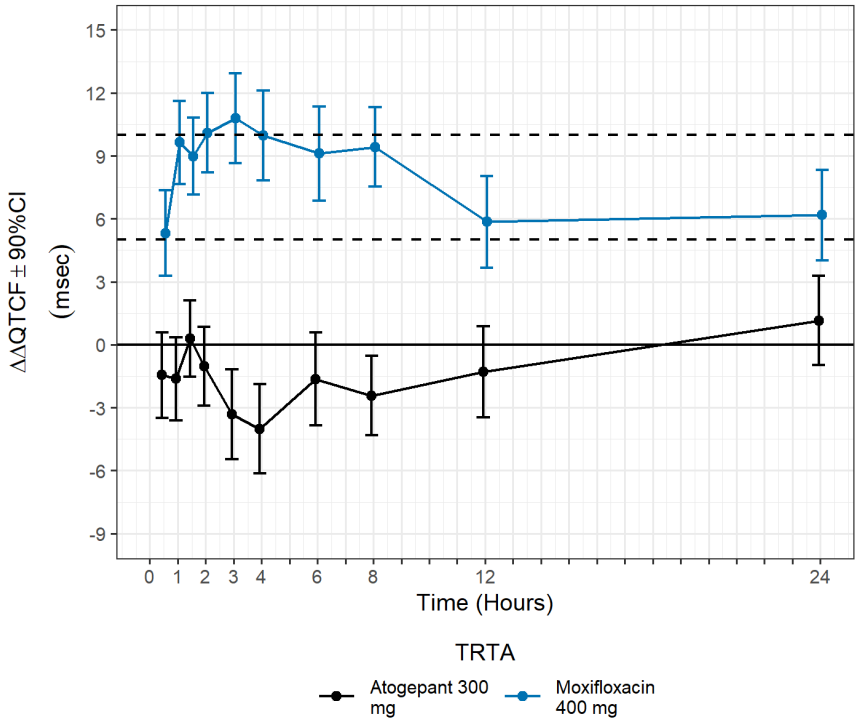


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Actual Treatment	Nact / Npbo	Time (Hours)	ΔΔQTCF (msec)	90.0% CI (msec)
Atogepant 300 mg	60 / 58	24.0	1.2	(-1.0 to 3.3)

4.3.1.1 Assay sensitivity

The same primary model was used for assay sensitivity. The time-course of changes in ΔΔQTc is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

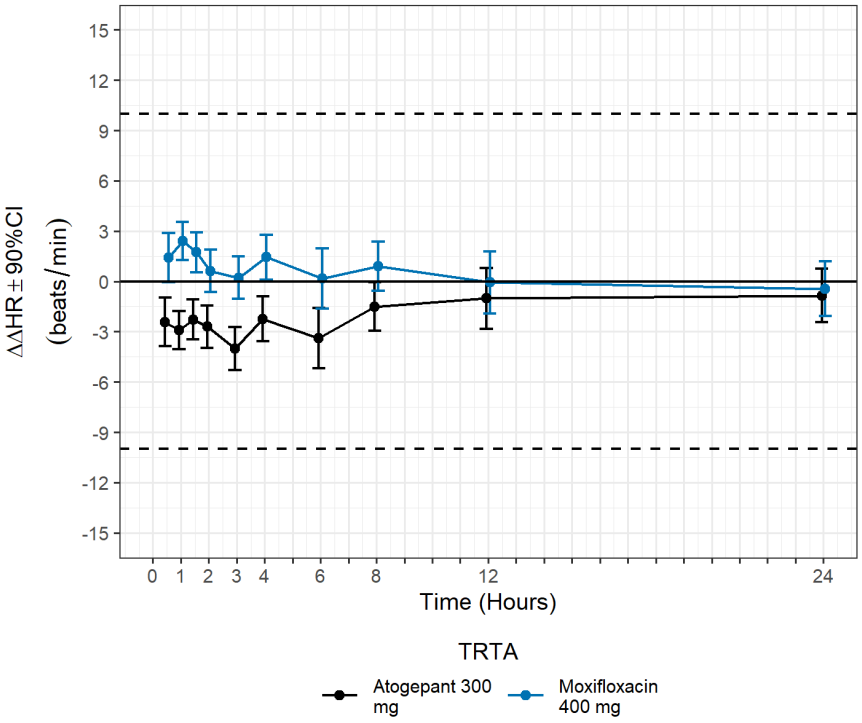
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTc

Actual Treatment	N	Time (hours)	ΔΔQTCF (msec)	90% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	59	3	10.8	(8.7, 12.9)	(7.9, 13.7)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

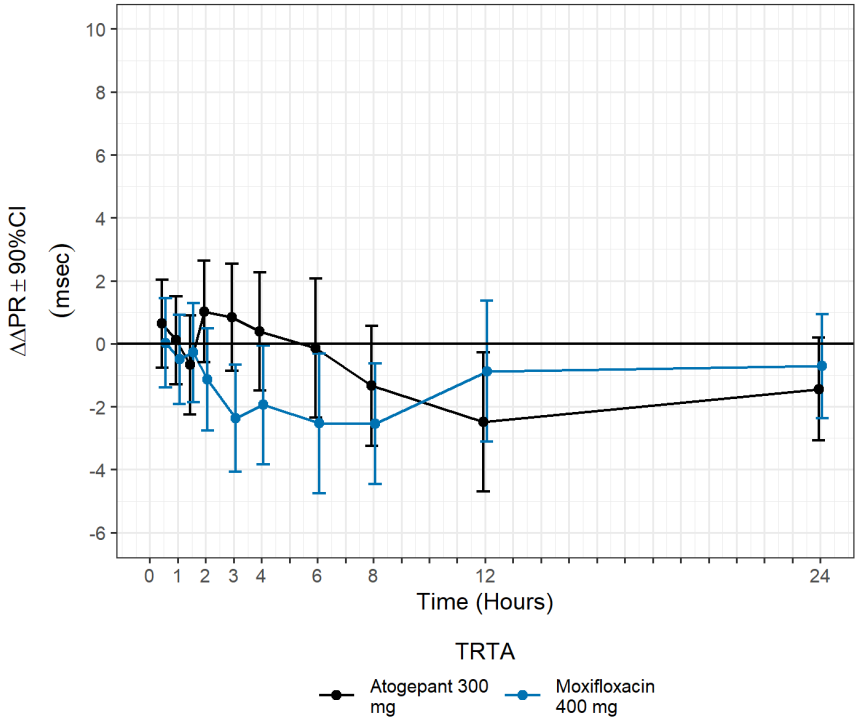
Figure 2: Mean and 90% CI of ΔΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

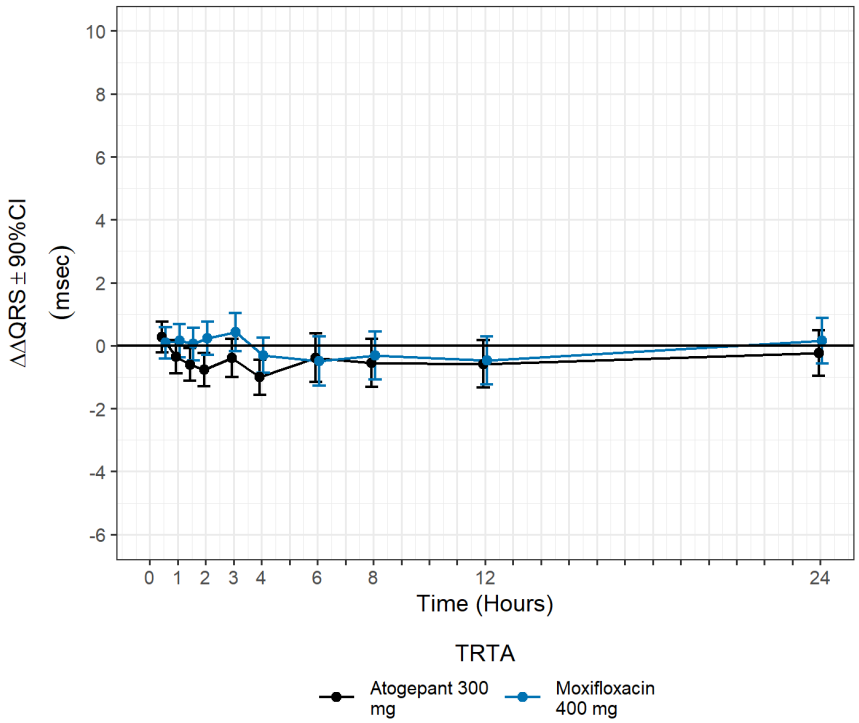
Figure 3: Mean and 90% CI of ΔΔPR Time Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF > 480 msec or ΔQTcF > 30 msec

4.4.2 HR

None of the subjects experienced HR > 100 bpm.

4.4.3 PR

None of the subjects experienced PR > 220 msec.

4.4.4 QRS

None of the subjects experienced QRS > 120 msec.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug-concentration and QTc using a linear model, the three key assumptions of the model needs to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) a lack of delay between plasma concentration and ΔΔQTc and 3) absence of non-linear relationship.

Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and Figure 5 evaluates the time-course of drug-concentration and ΔΔQTc and do not appear to show significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTc and supports the use of a linear model.

Figure 5: Time course of drug concentration (top) and QTc (bottom)

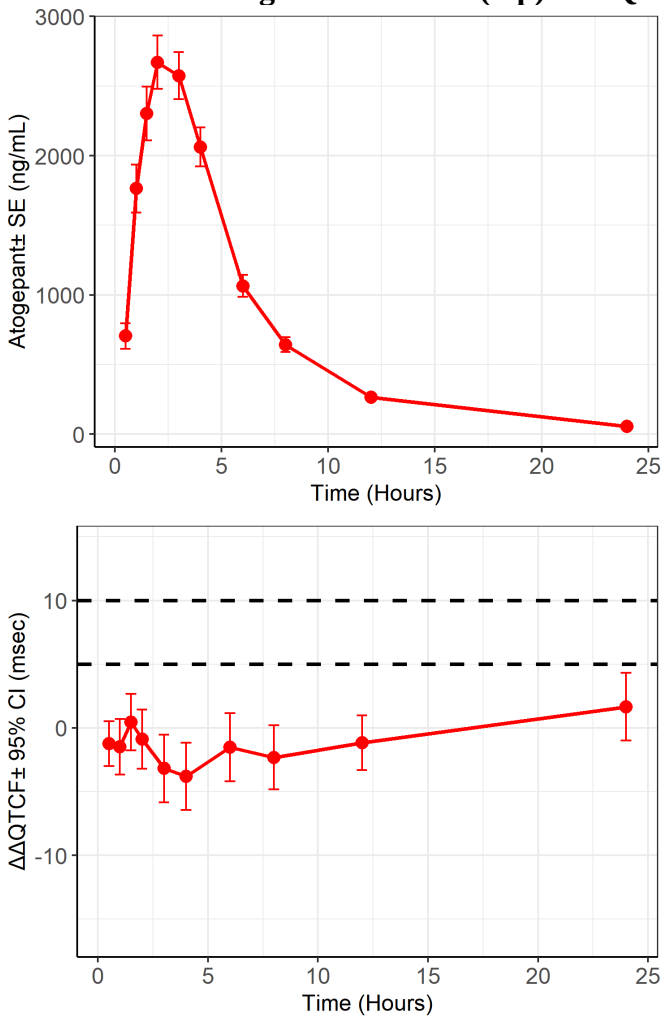
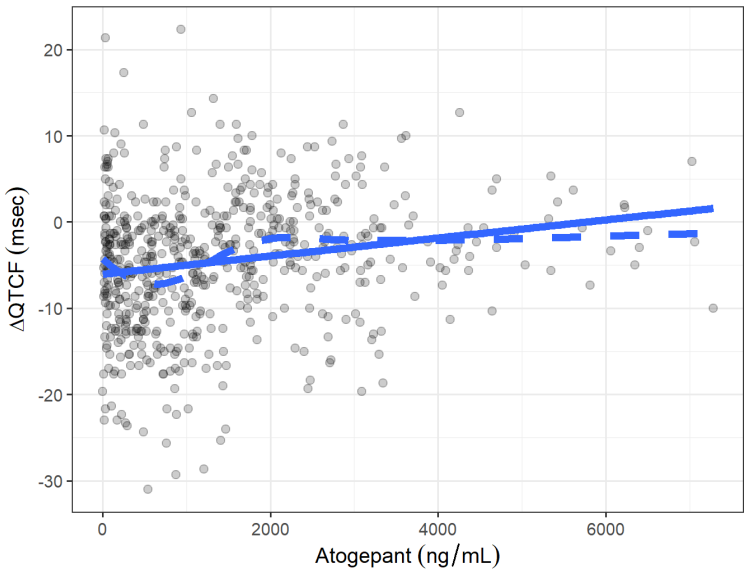


Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 4.

Figure 7: Goodness-of-fit plot for QTc

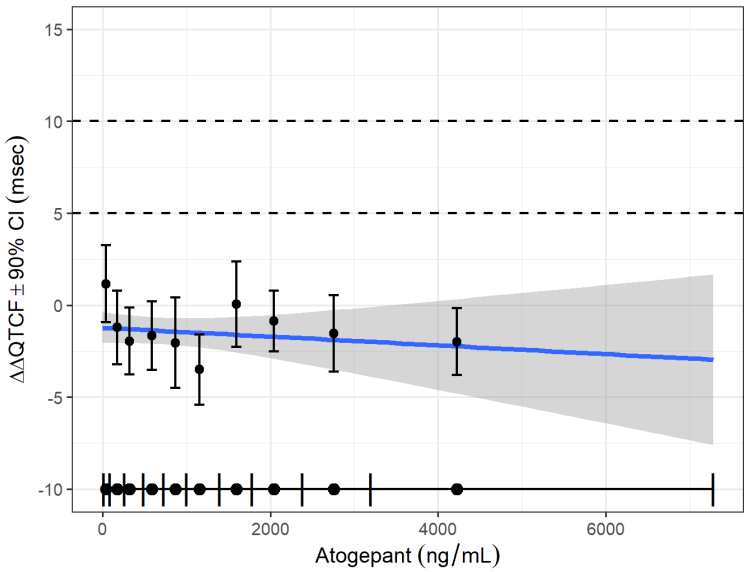


Table 4: Predictions from Concentration-QTcF Model

Treatment	Concentration (ng/mL)	ΔΔQTCF	90% CI
Atogepant 300 mg	2,870	-1.9	(-3.6 to 0.2)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NAN ZHENG
03/26/2021 01:44:49 PM
Hezhen Wang is the primary clinical pharmacology reviewer.

HEZHEN WANG
03/26/2021 02:47:46 PM

YU YI HSU
03/26/2021 04:36:48 PM

DALONG HUANG
03/26/2021 04:40:59 PM

MICHAEL Y LI
03/26/2021 07:03:49 PM

LARS JOHANNESEN
03/29/2021 08:23:42 AM

CHRISTINE E GARNETT
03/29/2021 08:32:43 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Anti-Infectives (DAI) Consult

Date of Consult Request: 02/18/2021
Requested Due Date: 03/21/2021
Requesting Individual / Division: Daniel Ngembus, RPM, Division of Neurology 2
NDA: 215206
Applicant: Abb Vie
Product and Dosage Form: atogepant, 10 mg, 30 mg, 60 mg oral tablets
Clinical Officer Responding: Elizabeth Story-Roller, M.D.
Clinical Team Leader: Edward Weinstein, M.D., Ph.D.
Deputy Director: Dmitri Iarikov, MD, PhD

Reason for Consult: DAI's clinical assessment of a fatal toxic shock event due to Group A beta hemolytic streptococcal (GAS) infection.

Information Reviewed:

1) Autopsy report from (b) (4)
2) Case Report for subject (b) (6)
3) Relevant scientific literature

Background:

The Division of Neurology 2 is currently reviewing NDA 215206 for atogepant, a small molecule CGRP receptor antagonist, (b) (4) Other molecules in this drug class (such as telcagepant and MK-3207) are known to cause drug-induced liver injury (DILI). The review division is seeking a consultative review from DAI regarding study subject (b) (6), study 3101-302-002, who died as a result of toxemia from a Group A beta hemolytic streptococcal (GAS) infection. This SAE occurred in a 26-year-old African American female patient who developed a mild influenza like illness (ILI) 4 days after initiating treatment with atogepant that left her bedridden for several days with fever and myalgia. The ILI resolved after 4 days. On study day 29, she was noted to have elevated ALT/AST and CPK without clear associated symptoms of liver dysfunction. On Day 43 the patient experienced chest pain and became unresponsive. She required CPR on the way to the hospital and was resuscitated, but then went into cardiac arrest later in the day and died. The autopsy report stated that she died from GAS infection, with postmortem cultures positive for GAS from the spleen, lung, and blood.

Consult Questions for DAIP:

1. Please provide input as to whether this clinical history is consistent with toxic shock syndrome related to the organism, and/or how the finding of Group A beta hemolytic streptococcal in her various organs at autopsy may be related to her clinical course prior to death.

DAI Response:

Despite this being an atypical case, this patient's clinical history does appear to be consistent with streptococcal toxic shock syndrome (STSS) related to invasive group A streptococcal infection.

Per the autopsy report, postmortem cultures grew GAS from spleen, lung, and blood. There was no mention of an overt skin or soft tissue infection or other potential nidus. Therefore, the fact that lung cultures were positive supports GAS pneumonia (PNA) as the most likely source. Although GAS is an uncommon causative pathogen, most cases of GAS PNA are community-acquired and occur in immune competent hosts. GAS PNA also tends to be aggressive, with approximately 80% of cases leading to bacteremia and a case fatality rate of 38%.[1]

Of significance, this patient developed a flu-like illness on study day 4 and was reportedly "bedridden for several days with fever and myalgias." However, she did not seek medical care and presumably was not tested for influenza or other respiratory viruses. Patients with a recent history of respiratory viral infection are at increased risk for bacterial superinfections, including GAS.[2] Although the five-week delay from the inciting viral illness in this case may have been somewhat prolonged, she may still have been at increased risk for a secondary bacterial pneumonia.

Approximately one third of invasive GAS infections lead to development of STSS.[3,4] TSS is defined by rapid onset (within hours) of shock/hypotension and multiorgan failure. The mortality rate for TSS ranges from 30-70% despite aggressive treatment.[5] This patient reportedly "felt fine" a day prior to onset of symptoms, but subsequently developed chest pain and shortness of breath the next morning, with rapid clinical deterioration and cardiac arrest within hours of symptom onset. Although this is an example of a severe case, it could certainly be consistent with the typical clinical course of invasive GAS infection/TSS.

2. Please provide input about the risk of Group A beta hemolytic streptococcal infection in patients with underlying liver injury

---

[1] Muller et al. Clinical and epidemiologic features of group a streptococcal pneumonia in Ontario, Canada. Arch Intern Med. 2003 Feb 24;163(4):467-72.

[2] Okamoto S, Nagase S. Pathogenic mechanisms of invasive group A Streptococcus infections by influenza virus-group A Streptococcus superinfection. Microbiol Immunol. 2018 Mar;62(3):141-149.

[3] Ekelund et al. Reemergence of emm1 and a changed superantigen profile for group A streptococci causing invasive infections: results from a nationwide study. J Clin Microbiol. 2005 Apr;43(4):1789-96.

[4] Svensson et al. Invasive group A streptococcal infections in Sweden in 1994 and 1995: epidemiology and clinical spectrum. Scand J Infect Dis. 2000;32(6):609-14.

[5] Nelson et al. Epidemiology of Invasive Group A Streptococcal Infections in the United States, 2005-2012. Clin Infect Dis. 2016 Aug 15;63(4):478-86.

DAI Response:

This patient did have a significant bump in her ALT, AST, and CPK on study day 29, at which time the study drug was stopped. Her liver tests continued to increase slightly through day 33, but subsequently improved to near normal levels by day 40—three days prior to onset of symptoms related to GAS infection. Throughout the study, the patient's bilirubin and alkaline phosphatase remained normal. She also exhibited no evidence of synthetic dysfunction during this time, with normal INR values throughout and no apparent encephalopathic symptoms.

Although acute liver failure can increase risk of bacterial infections,[6,7] this is more commonly seen in acute-on-chronic liver failure due to impaired immune response.[8]

As stated above, this patient most likely developed a primary GAS pneumonia, which led to bacteremia and TSS. Although she had few intrinsic risk factors for GAS infection, her history of flu-like illness several weeks prior may itself have increased her risk of bacterial superinfection.

Based on this patient's clinical course, including improvement in her liver tests prior to onset of infection, lack of evidence of synthetic dysfunction, and potential pulmonary risk factors, it seems unlikely that this patient's suspected drug-induced liver injury significantly contributed to her overwhelming GAS infection and subsequent death.

[6] Rolando et al. Bacterial and fungal infection in acute liver failure. Semin Liver Dis. 1996 Nov;16(4):389-402.

[7] Pyleris et al. Pathophysiology and management of acute liver failure. Annals of Gastroenterology, North America 2010; 23:257–265.

[8] Bunchorntavakul et al. Bacterial infections in cirrhosis: A critical review and practical guidance. World J Hepatol. 2016;8(6):307-321.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARMEN L DEBELLAS
02/26/2021 04:22:47 PM

ELIZABETH R STORY-ROLLER
02/26/2021 04:28:40 PM

EDWARD A WEINSTEIN
02/26/2021 04:30:04 PM

DMITRI IARIKOV
02/26/2021 04:47:20 PM